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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/547,501 | 04/12/2000 | Samuel T. Christian | IMI-001 | 6126 |

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John S Sundsmo
BioMedPatent.Com
P.O. Box 535
vista, CA 92085

| EXAMINER | |
|---|---|
| JIANG, SHAOJIA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/547,501 | CHRISTIAN, SAMUEL T. | |
| | Examiner | Art Unit | |
| | Shaojia A. Jiang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 August 2004 and 27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-16,19 and 21-42* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-9 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,10-16,19 and 21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 30, 2004 has been entered.

This Office Action is in response to Applicant's request for continued examination (RCE) filed August 30, 2004, and amendment and response to the Final Office Action (mailed February 26, 2004), filed August 30, 2004, September 7, 2004 and September 27, 2004 wherein claims 5, 17-18 and 20 are canceled; claims 4, 10-16, 19, 21-40, and 41 have been amended.

As recorded in the previous Office Action February 26, 2004, Claims 1-3 and 6-9, 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Currently, claims 4, 10-16, 19, 21-40, 41, and 1-3 and 6-9, 42 and are pending in this application.

Claims 4, 10-16, 19, 21-40, and 41 as amended now are examined on the merits herein.

Applicant's amendment filed September 27, 2004 with respect to the rejection of claims 1-12 made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitations, as Claim 10 recites the limitation "X and Y" in line 7 of the claim "each of X and Y, when present is a carbon atom, a halogen atom or a lower alkyl" and Claim 11 recites the limitation "comprising X and Y comprising a halogen";

Claim 11 recites the limitation "comprising X and Y comprising a halogen or oxygen" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim since claim 10 does not recited any X and Y being oxygen;

The recitation "selected from TABLE A or from TABLE B " in claims 41 renders the these claims indefinite. Applicant is requested to note that each claim must be self-contained;

In claim 21, a period is missing in this claim. According to MPEP 608.01(m) "Each claim begins with a capital letter and ends with a period";

In claim 23 that the recitation "a sugar is further selected from the group.." is not proper since Applicant is requested to note that a claim which depends from a claim, i.e., claim 22, which "consists of" the recited elements or steps cannot add an element or step; of record stated in the Office Action dated February 26, 2004 have been fully considered and found persuasive to remove the rejection as to these indefinite recitations.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 10-16, 19, 21-40, and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had full possession of the claimed invention.

Applicant's amendment submitted September 27, 2004 with respect to these amended claims have been fully considered but is deemed to insert new matter into the claims.

The omission of essential elements of the invention, "$R_5$, $R_{5'}$, $R_6$, $R_{6'}$, and Z" in claimed formula IV is deemed to raise new matter issue, i.e., an issue regarding whether the inventor had possession of a broader, more generic invention. See, e.g., >PIN /NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1248, 64 USPQ2d 1344, 1353 (Fed. Cir. 2002). As noted in MPEP 2163, A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement. See Gentry Gallery, 134 F.3d at 1480, 45 USPQ2d at 1503; In re Sus, 306 F.2d 494, 504, 134 USPQ 301, 309 (CCPA 1962).

In the instant case, the specification as originally filed discloses the "$R_5$, $R_{5'}$, $R_6$, $R_{6'}$, and Z" limitations at page 36 line 20 to page 37 line 3. In the absence of "$R_5$, $R_{5'}$, $R_6$, $R_{6'}$, and Z" for the structural formula IV, one skilled in the relevant art would not

recognize and understand the invention now claimed. Thus, that these limitations are deemed to are **essential and critical elements** of the claimed invention.

Moreover, Applicant's amendment submitted September 27, 2004 with respect to amended claim 10 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for "X an Y is nitrogen atom, a sulfur atom or an oxygen atom". Nowhere is these limitations be found in the specification.

Further, the omission of essential elements of the invention, "A" is the prodrug selected from those specific prodrugs in Table A or Table B in claimed formula I of claim 41 is deemed to raise new matter issue, i.e., an issue regarding whether the inventor had possession of a broader, more generic invention, **any** cyclic, heterocyclic, aryl or heteroaryl CNS-acting prodrugs.

The specification as originally filed does not provide adequate support for any compounds encompassed by a generic claim 41, the formula I herein. The specification fails to describe any specific compound having this formula I but merely mentions "Compound #1 and #2" in the Examples. The specification as originally filed fails to provide any structure, formula, [or] chemical name for "Compound #1 and #2".

The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added). See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997).

More importantly, the court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when... the evidence indicates ordinary artisans could not predict the operability .....of any other species." (see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274, Fed. Cir. 2004). The court of *Noelle v. Lederman* also pointed out that generic claim to anti-CD40CR Mabs lacked written description support because there was no description of anti-human or other species Mabs, an no description of human CD40CR antigen. The court further pointed out that attempt to "define an unknown by its binding affinity to another unknown" failed. See 355 F.3d 1343, 69 USPQ2d 1508, Fed. Cir. 2004.

Consequently, as discussed above there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claims 4, 10-16, 19, 21-40, and 41 are rejected under 35 U.S.C. 112, first paragraph, for lack of scope of enablement because, as discussed in the lack of written description rejection above, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method for improving the aqueous solubility and the blood brain barrier penetrability of a drug.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented:

As discussed in the lack of written description rejection above, the amount of direction or guidance is lacking.

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of

fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the methods herein.

The presence or absence of working examples and the quantity of experimentation necessary:

As discussed above, only two particular compounds "Compound #1 and #2" were tested in working examples. Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the compounds in the claimed method.

Since any significant structural variation to a compound would be reasonably expected to alter its properties, one of ordinary skill would be required to perform undue experimentation to determine which, if any, other compounds encompassed by the formula I or IV would be useful in the claimed composition for the particular treatment.

*Genentech*, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims in the claimed method to be administered to a host, with no assurance of success.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 10-16, 19, 21-40, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "$R_7$" in Formula I in claim 41, is not understood to one of ordinary skill in the art since there is no definition of "$R_7$" in Formula I herein. Therefore, the scope of claims is indefinite as to the method encompassed thereby.

The recitation "each of "-" in claim 41 is unclear as to what it represents.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4, 10-16, 19, 21-40, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Likhoshersfov et al. (of record) in view of Mizuma et al. (72 and 73, PTO-1449 submitted November 13, 2000) and Takata et al. (96, PTO-1449 submitted November 13, 2000), and Vannucci et al. (99, PTO-1449 submitted November 13, 2000).

Likhoshersfov et al. discloses the incorporation of carbohydrate residues into active compounds such as dopamine to form dopamine glycoconjugates, the instant elected species (see abstract).

Likhoshersfov et al. does not expressly disclose the employment of the particular incorporation of the particular claimed carbohydrate residues having formula claimed herein into specific active compounds (active drugs) such as dopamine glycoconjugates in a method for improving the aqueous solubility and blood brain barrier penetrability of a drug.

Mizuma et al. teaches that sugar-conjugated drugs such as glucose-conjugated compounds provide these compounds (drugs) with a new route by the way of the glucose transport carrier for better absorption in intestine, improving the poorly absorbable drugs (see abstract).

Both Takata et al. and Vannucci et al. teach the transport of glucose across the blood-tissue barriers such as blood-brain barrier (see abstracts and the entire articles).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ conjugates of carbohydrate residues and active compounds (active drugs) such as dopamine glycoconjugates in a composition and a method for improving the aqueous solubility and blood brain barrier penetrability of a drug.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ conjugates of carbohydrate residues and active compounds (active drugs) such as dopamine glycoconjugates in a composition and a

method for improving the aqueous solubility and blood brain barrier penetrability of a drug, since active compounds (active drugs) such as dopamine glycoconjugates are known according to Likhoshersfov et al. Moreover, the teachings of Mizuma et al., Takata et al. and Vannucci et al. have provided the motivation to make conjugates of carbohydrate residues and active drug compounds herein since sugar-conjugated drugs such as glucose-conjugated compounds provide these compounds (drugs) with a new route by the way of the glucose transport carrier for better absorption in intestine and improving the poorly absorbable drugs, and also enhancing the blood brain barrier penetrability of a drug.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

***Response to Argument***

Applicant's arguments filed August 30, 2004 and September 7, 2004 with respect to the rejection made under 35 U.S.C. 103(a) of record in the previous Office Action dated February 26, 2004 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

First, Applicant attacks each cited reference and asserts that no motivation and expectation of success are provided by the cited references. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

In this case, Likhoshersfov et al. discloses the incorporation of carbohydrate residues into active compounds such as dopamine to form dopamine glycoconjugates, the instant elected species. Thus, the active compounds (active drugs) such as dopamine glycoconjugates are known according to Likhoshersfov et al. Moreover, the teachings of Mizuma et al., Takata et al. and Vannucci et al. have provided the motivation to make conjugates of carbohydrate residues in general and active drug compounds herein since sugar-conjugated drugs such as glucose-conjugated compounds provide these compounds (drugs) with a new route by the way of the glucose transport carrier for better absorption in intestine and improving the poorly absorbable drugs, and also enhancing the blood brain barrier penetrability of a drug.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

Moreover one of ordinary skill in the art would question the *enablement* issue for the instant prodrug compound incorporating with numerous drugs in Table A and B encompassed in the claims, whose structures differ completely or substantially. Further, **biological activities, chemical stability and side effects, and possible toxicity** resulting from the instant resultant compounds would also be in question.

It is noted that only two particular compounds, Compound 1 and 2 are disclosed in working examples of the specification. Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of the prodrug compounds incorporating with numerous drugs in Table A and B encompassed in the

claims. Therefore, Applicant's Examples of the specification have been fully considered but are not deemed persuasive as to the nonobviousness and/or unexpected results of the claimed invention over the prior art since the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the ingredients in the claimed method. See MPEP § 716.02(d). Further, the specification does not provide testing results for biological activities, chemical stability and side effects, and possible toxicity of the instant resultant compounds.

Note that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The burden is shifted to Applicant to show factually supported objective evidence to rebut the prima facie case of obviousness over the prior art.

Therefore, the evidence presented in specification herein is not seen to be clear and convincing in support the nonobviousness of the instant claimed invention over the prior art.

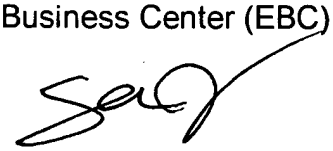
For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
July 14, 2005